APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,695	06/08/2001	John R. Desjarlais	16380-002001	8902

26161　　7590　　07/26/2004	EXAMINER
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110	MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)
Office Action Summary	09/877,695	DESJARLAIS, JOHN R.
	Examiner	Art Unit	
	Marjorie A. Moran	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE __3__ MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed
  after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
  Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any
  earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is
closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8, 12-66* is/are pending in the application.

  4a) Of the above claim(s) *15,17,23,30-37,57-59,62,63 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12-14,16,18-22,24-29,38-56,60,61,64 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/30/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

  a)☐ All b)☐ Some * c)☐ None of:

  1.☐ Certified copies of the priority documents have been received.

  2.☐ Certified copies of the priority documents have been received in Application No. _____.

  3.☐ Copies of the certified copies of the priority documents have been received in this National Stage
  application from the International Bureau (PCT Rule 17.2(a)).

  * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
  Paper No(s)/Mail Date *1/02, 2/03, 11/03*.

4)☐ Interview Summary (PTO-413)
  Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

Election/Restriction

Applicant's election without traverse of Group I, claims 1-29 and species of Monte Carlo design algorithm, an ensemble of backbone proteins generated by a Monte Carlo simulation in the reply filed on 3/29/04 is acknowledged. As a search for a Monte Carlo design algorithm was coextensive with a search for mean field theory algorithm, the species of mean field theory has been rejoined with the species of Monte Carlo algorithm with regard to the species of protein design algorithm.

Newly submitted claims 57-59, 62-63 and 66 are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons:

Claims 57-59 and 66 are directed to methods and products for performing methods comprising steps and results not recited in the method of Group I, and are therefore separate and distinct from Group I;

Claims 62-63 are directed to products not produced or used in the method of Group I.

Claims 57-59, 62-63 and 66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim. In addition, claims 15, 17, 23, and 30-37 are withdrawn from consideration as being directed to a non-elected species or Invention. Election was made **without** traverse in the reply filed on 3/29/04.

An action on the merits of elected claims 1-8, 12-14, 16, 18-22, 24-29, 38-56, 60-61 and 64-65, as they read on the elected specie, follows.

Information Disclosure Statement

The IDS's filed 1/11/02, 2/7/03, and 11/24/03 have been considered in full.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8, 12-16, 18-20, 22, 24-26, 28-29, 38-56 and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a step of "sampling or evaluating" amino acids or rotamers "within the context" of a protein sequence (or sequences) and a backbone structure. Claim 19 recites a step of "evaluating" fitness of amino acids "within the context" of a protein sequence and structure. Claim 56 also recites "evaluating" fitness of rotamers "within the context" of a protein sequence and spatial constraint. It is unclear what is meant by "sampling" or "evaluating" amino acids or rotamers within "the context" of a protein sequence and structure or spatial constraint. Does applicant intend to take actual samples of amino acids or peptide structures (rotamers), or does applicant intends to do something (e.g. in silico steps) with amino acid or rotamer coordinates or other computer representations? Further, it is unclear what method steps or limitations are intends by "in the context" of a protein sequence and backbone structure or

spatial constraint. Does applicant intend a comparison of some sort; e.g. an alignment, or identity or homology determination? Or does applicant intend a fitting or docking-type of calculation? Or does applicant intend a calculation of energy configurations or application of an algorithm in determining addition of amino acids or rotamers to a backbone to generate a protein structure? As it is unclear what steps and/or limitations are intended by the "sampling" or "evaluating" steps of claims 1 and 51, the claims are indefinite.

Claims 3, 26, 60 and 61 each recites a step of generating or producing a protein or library of proteins from a probability matrix. It is unclear if applicant intends to generate actual proteins (e.g. from a protein synthesizer), or intends to generate a list of protein sequences (i.e. a virtual library) identified or designed by the matrix of claims 1 and 19. Applicant is advised that a step of actually synthesizing proteins directly from a matrix is not supported or enabled by the instant specification; however, as applicant's intended limitation is unclear, the claims are rejected herein only for indefiniteness. It is noted that claim 25, which clearly recites generation of a protein *sequence*, is definite.

Claims 8, 18, 29, 51 recite limitations which "satisfy" a constraint or constraints. It is unclear what conditions must be met to "satisfy" a constraint; i.e. must some limit or threshold be met, or exceeded, or must an energy level be below a certain limit, etc.? As the metes and bounds intended by applicant by the term "satisfy" as applied to a constraint, are unclear, the claims are indefinite.

Claims 39-40 limit a library to be "designed by" various procedures. It is unclear what structural limitation of the library elements is intended by the

"design" limitations. If applicant intends to limit the method of claim 26, and thereby parent claim 19, then it is unclear what method step is intended to be limited, or whether applicant intends further method steps. It is noted that parent claim 26 is directed to *producing* a library, and does not recite a design step. Claim 19, from which claim 26 depends, also fails to recite a design step. If applicant intends to limit the method of claim 19 or claim 26 to comprise *further* method steps, then applicant is advised to clearly indicate this intention and to recite any method steps using active, positive claim language.

Claim 44 limits the method of claim 1 to comprise freezing side chain identities and rotamers at "all other positions" in the protein. As no individual "position" or "positions" are identified in claim 1, it is unclear what "other positions" are intended to be frozen in claim 44, therefore the claim is indefinite. For purposes of search, this claim is interpreted to recite that rotamers and/or side chains may be evaluated individually.

Claim 48 limits the method of claim 3 to further comprise screening or selecting one or more proteins from the generated combinatorial library. However, claim 48 does not recite any parameters fro screening or selecting, such that one skilled in the art would be apprised of the metes and bounds intended by applicant for the protein to be thus chosen. As is it unclear what the protein in intended to be selected or screened for (or against), the claim is indefinite.

The terms "enhanced" and "improved" in claim 50 are relative terms which renders the claim indefinite. The term terms "enhanced" and "improved" are not

defined by the claim, the specification does not provide a standard for

ascertaining the requisite degree, and one of ordinary skill in the art would not be

reasonably apprised of the scope of the invention. It is not clear what the

proteins are intended to be "enhanced" or "improved" relative to. In addition, it is

not clear what is intended by an "enhanced" activity (e.g. a higher binding affinity

may be considered "enhanced" for an compound which acts as a receptor

agonist whereas a lower binding affinity would be considered "enhanced" for an

antagonist). Nor is it clear what is intended for an "improved" stability (e.g. for a

drug wherein a faster clearance rate is desired, a compound with a lower stability

may be considered "improved"). For these reasons, the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35

U.S.C. 102 that form the basis for the rejections under this section made in this

Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-8, 12-14, 18-21, 27-29, 41-47, 49, 51-56, and 64-65 are

rejected under 35 U.S.C. 102(b) as being anticipated by KOEHL et al. (J. Molec.

Biol. (1994) vol. 239, pp. 249-275).

KOEHL teaches a computerized method of generating a global

conformational (probability) matrix representing a protein structure (p. 250)

wherein an averaged rotamer (backbone) library or ensemble is provided (p.

251), a self consistent mean field theory/algorithm (SCFM) is used to generate

possible side chain sequences and to evaluate all possible rotamers in "the

context" of the backbones and side chain sequences to generate the matrix (pp.

251-252 and 256-257), thus anticipating claims 1, 5, 19 and 44, and 65. KOEHL

teaches that the protein and/or backbones may be derived from or based on

comparison to a natural protein (pp. 254-255), thus anticipating claims 6-7, 14,

20-21, and 27-28. KOEHL further teaches that her matrix calculations comprise

information from partition functions (p. 254) and comprise information for all

amino acids (p. 259, esp. Table 3), thereby anticipating claims 45 and 47.

KOEHL teaches that his method steps may be iterated in multiple cycles, using

multiple matrices, until convergence is reached (e.g.; p. 254), and teaches

addition and subtraction of free energy to meet accuracy constraints (pp. 254-

258), thus anticipating claims 4, 8, 12-13, 18, 29, 41-43, 46, 49, and 51-56.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for

all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or
> described as set forth in section 102 of this title, if the differences between the subject
> matter sought to be patented and the prior art are such that the subject matter as a whole
> would have been obvious at the time the invention was made to a person having ordinary
> skill in the art to which said subject matter pertains. Patentability shall not be negatived
> by the manner in which the invention was made.

Claims 1, 4-8, 12-14, 16, 18-22, 24, 27-29, 41-47, 49, 51-56 and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over KOEHL et al. (J. Molec. Biol. (1994) vol. 239, pp. 249-275) in view of KOEHL et al. (Current Opinion Struct. Bio. (1996) vol. 6, pp. 222-226).

KOEHL (1994) teaches a computerized method of generating a global conformational (probability) matrix representing a protein structure, as set forth above. KOEHL does not teach a Monte Carlo algorithm to generate an ensemble of proteins.

KOEHL (1996) teaches a mean field Monte Carlo procedure to generate a family (ensemble) of proteins, and teaches that this provides significant improvement in an SCMF method of modeling proteins (p. 224).

It would have been obvious to one of ordinary skill in the art at the time of invention to have included the Monte Carlo generation of KOEHL (1996) in the method of KEOHL (1994) where the motivation would have been to improve the SCMF method of modeling proteins, as taught by KOEHL.

Claims 2-3, 25-26, 38-40, 48, 50, and 60-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over KOEHL et al. (J. Molec. Biol. (1994) vol. 239, pp. 249-275) in view of KOEHL et al. (Current Opinion Struct. Bio. (1996) vol. 6, pp. 222-226) as applied to claims 1, 4-8, 12-14, 16, 18-22, 24, 27-29, 41-43, 46-47, 49, 51-56 and 64-65 above, and further in view of DAHIYAT et al. (Protein Sci. (1996) vol. 5, pp. 895-903).

KOEHL and KOEHL teach and make obvious a computerized method of generating a global conformational (probability) matrix representing a protein structure, as set forth above.   Neither KOEHL teaches generation or selection of a protein or proteins generated/designed by the method.

DAHIYAT teaches a method of designing proteins from a backbone and rotamer library using a Monte Carlo algorithm (p. 901) and teaches selection and synthesis of the peptide library designed (p. 902). DAHIYAT teaches that proteins may be selected for stability (p. 895:Abstract).

It would have been obvious to one of ordinary skill in the art at the time of invention to have selected and synthesized peptides, as taught by DAHIYAT which were generated in the method of KOEHL and KOEHL, where the motivation would have been to compare predicted to actual activity and stability of the peptides, as taught by DAHIYAT (abstract and p. 902).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Mon. to Wed, 7:30-4; Thurs 7:30-6; Fri 7-1 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571)272-0722.

The fax phone number for the organization where this application or proceeding

is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from

the Patent Application Information Retrieval (PAIR) system. Status information

for published applications may be obtained from either Private PAIR or Public

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direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-

free).

Marjorie A. Moran
Primary Examiner
Art Unit 1631

7/21/04